Outcome of men with relapse after adjuvant carboplatin for clinical stage I seminoma

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Abstract: Purpose Adjuvant carboplatin is one of three management strategies that may follow inguinal orchiectomy in clinical stage I seminoma. However, little is known about the outcome of patients who experience a relapse after such treatment. Patients and Methods Data from 185 patients who relapsed after adjuvant carboplatin between January 1987 and August 2013 at 31 centers/groups from 20 countries were collected and retrospectively analyzed. Primary outcomes were disease-free survival and overall survival. Secondary outcomes were time to, stage at, and treatment of relapse as well as rate of subsequent relapses. Results With a median follow-up of 53 months (95% CI, 48 to 60 months) the 5-year disease-free survival was 82% (95% CI, 77% to 89%), and the 5-year overall survival was 98% (95% CI, 95% to 100%). The median time from orchiectomy to relapse was 19 months (95% CI, 17 to 23 months); 15% (95% CI, 10% to 21%) of relapses occurred > 3 years after treatment. The majority of relapses were detected by computed tomography scan during routine follow-up, 98% in the International Germ Cell Cancer Collaborative Group good prognosis group. Chemotherapy was administered to 92% of patients, mostly as standard first-line treatment corresponding to stage; 8% of patients had additional local treatments. Only 28 patients experienced a second relapse. At last follow-up, 174 (94%) of 185 patients were alive without disease, and four patients with disease. Seven patients died, three of whom due to progressive disease. Conclusion Within the limitations of a retrospective analysis, the results suggest that the majority of patients who experience a relapse after adjuvant carboplatin for clinical stage I seminoma can be successfully treated with a cisplatin-based chemotherapy regimen adequate for stage. Because 15% of the relapses occurred > 3 years after adjuvant treatment, a minimum of 5 years follow-up is recommended.

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ORIGINAL REPORT

Outcome of Men With Relapse After Adjuvant Carboplatin for Clinical Stage I Seminoma

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ABSTRACT

Purpose

Adjuvant carboplatin is one of three management strategies that may follow inguinal orchiectomy in clinical stage I seminoma. However, little is known about the outcome of patients who experience a relapse after such treatment.

Patients and Methods

Data from 185 patients who relapsed after adjuvant carboplatin between January 1987 and August 2013 at 31 centers/groups from 20 countries were collected and retrospectively analyzed. Primary outcomes were disease-free survival and overall survival. Secondary outcomes were time to, stage at, and treatment of relapse as well as rate of subsequent relapses.

Results

With a median follow-up of 53 months (95% CI, 48 to 60 months) the 5-year disease-free survival was 82% (95% CI, 77% to 89%), and the 5-year overall survival was 98% (95% CI, 95% to 100%). The median time from orchiectomy to relapse was 19 months (95% CI, 17 to 23 months); 15% (95% CI, 10% to 21%) of relapses occurred > 3 years after treatment. The majority of relapses were detected by computed tomography scan during routine follow-up, 98% in the International Germ Cell Cancer Collaborative Group good prognosis group. Chemotherapy was administered to 92% of patients, mostly as standard first-line treatment corresponding to stage; 8% of patients had additional local treatments. Only 28 patients experienced a second relapse. At last follow-up, 174 (94%) of 185 patients were alive without disease, and four patients with disease. Seven patients died, three of whom due to progressive disease.

Conclusion

Within the limitations of a retrospective analysis, the results suggest that the majority of patients who experience a relapse after adjuvant carboplatin for clinical stage I seminoma can be successfully treated with a cisplatin-based chemotherapy regimen adequate for stage. Because 15% of the relapses occurred > 3 years after adjuvant treatment, a minimum of 5 years follow-up is recommended.

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INTRODUCTION

Approximately three quarters of patients with pure seminoma of the testis present with clinical stage I (CSI), defined as disease limited to the testis with normal serum tumor markers and no evidence of local or distant metastases after inguinal orchiectomy.[1,2] Three different management strategies—active surveillance, adjuvant para-aortic radiation, and adjuvant chemotherapy with carboplatin—can be pursued after surgery. Each strategy provides a similarly excellent 5-year survival of approximately 98%, but they differ in their relapse rate and their need for further treatment.[3]

Relapses are observed among ≥ 20% of patients who undergo active surveillance, particularly if risk factors for occult metastatic disease are present. Adjuvant treatment with either radiotherapy or carboplatin can substantially reduce this risk. In a large prospective randomized trial, relapse rates and survival probabilities were similar with adjuvant radiotherapy or carboplatin for CSI

ASSOCIATED CONTENT

Appendix
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Data Supplement
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seminoma.[4,5] However, because of the ease of administration, quicker recovery from adverse effects of adjuvant treatment, and the known long-term risks for induction of secondary malignancies after adjuvant radiotherapy,[6-8] adjuvant carboplatin has been favored over adjuvant radiotherapy, which is no longer recommended as a standard option.[3,9] As a result of insufficient follow-up, no data are available yet with respect to long-term toxicities and the potential induction of secondary malignancies after adjuvant carboplatin.

After adjuvant carboplatin in CSI seminoma, a relapse rate of approximately 4% to 9% has been reported.[4,5,10-12] The timing and location as well as the treatments and respective outcomes of such relapses have not been exclusively studied so far. In particular, whether the prognosis of patients with relapse is compromised by previous adjuvant treatment remains unclear. Because a prospective trial unlikely will ever be conducted in this patient population, we retrospectively collected data from 31 centers/groups worldwide to analyze time to and stage at relapse, mode of detection, and the treatments patients received and their respective outcomes.

PATIENTS AND METHODS

We contacted centers worldwide, mostly through the network of the Global Germ-Cell Cancer Group, and explored whether they had treated patients with CSI seminoma and a relapse after one or two cycles of adjuvant carboplatin. Focus of the analysis was solely on patients with unequivocal relapse after adjuvant carboplatin. After identification of suitable cases, detailed information on patients was collected through predefined structured questionnaires. The protocol for the analysis and the case report forms are provided in the Data Supplement. Approval of the local ethics committee was obtained before the retrospective data collection.

Information was collected on patient characteristics at the time of treatment with carboplatin; methods used for dosing of carboplatin; and time to, detection of, and location of relapse. Data on imaging modalities, elevation of tumor markers at time of relapse, and treatment of relapse (surgery, radiotherapy, chemotherapy, or combination) as well as outcome of this treatment were gathered. If applicable, data about further relapses and treatment modalities of subsequent relapses were obtained as was the cause of death, if applicable. Data were collected and anonymized locally and subsequently transferred and entered into a joint database in St Gallen, Switzerland.

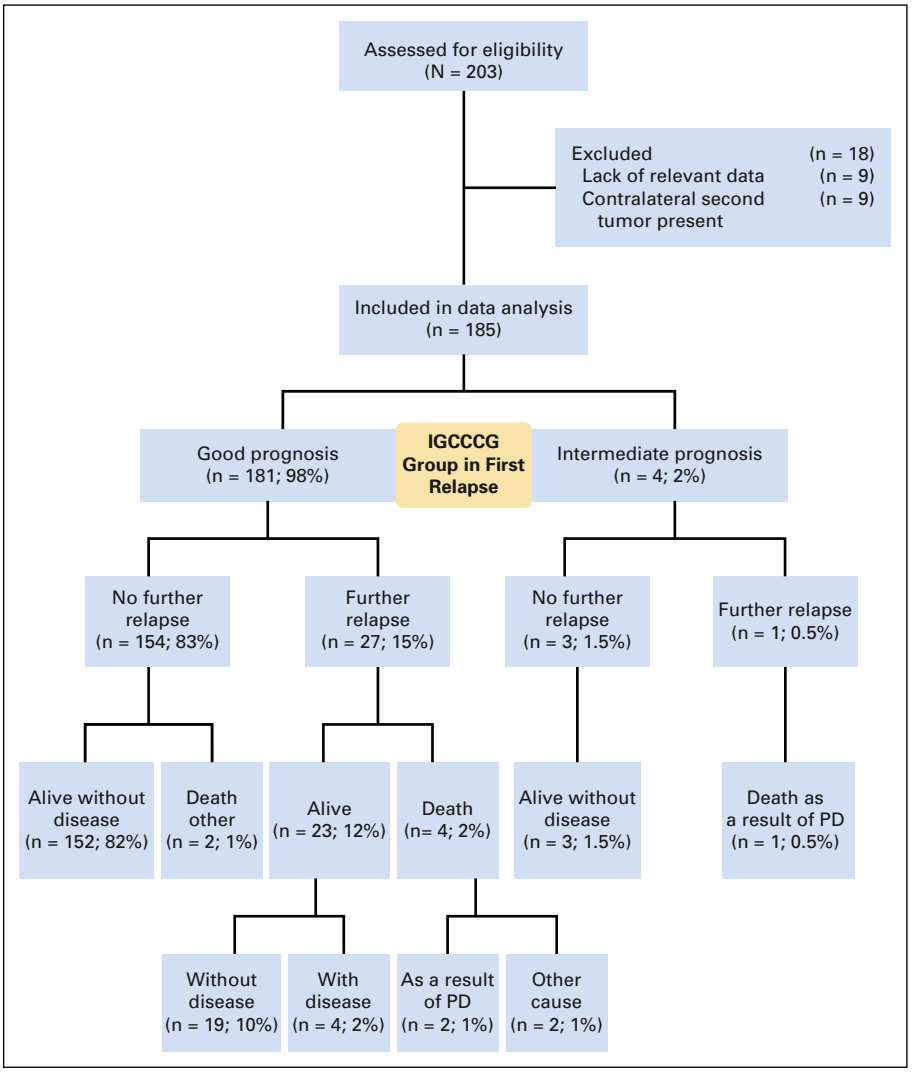

Fig 1. Overview of patients. IGCCCG, International Germ Cell Cancer Collaborative Group; PD, progressive disease.

Patients

Inclusion criteria were male sex, age 18 years and older, pure seminoma at initial histology, CSI, and normal value of the tumor marker alpha-fetoprotein at initial diagnosis. Further conditions for inclusion were orchiectomy for seminoma, one or two cycles of adjuvant carboplatin, and clinical or radiologic confirmation of recurrent seminoma.

Exclusion criteria were other malignancies that required cytotoxic therapy during the time of follow-up, nonseminoma histology or any other histology apart from pure seminoma at initial diagnosis, treatment with more than two cycles of adjuvant carboplatin, and elevated levels of alpha-fetoprotein at initial diagnosis. Disease stage was reported according to the International Union Against Cancer classification,[13] and for allocation to risk categories, the International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic classification[14] was used.

Statistical Analysis

Data of 185 patients who had received adjuvant treatment with carboplatin between January 1987 and August 2013 in 31 centers/groups from 20 countries and who had experienced a relapse were retrospectively analyzed. Primary end points were overall survival (OS) and disease-free survival (DFS). Secondary outcomes were time to relapse, stage at relapse, management strategies chosen, and rates of subsequent relapses. Time-to-event end points were analyzed by the Kaplan-Meier method. Calculation of time to relapse started with the date of orchiectomy. Calculation of time to subsequent relapse started with the date of diagnosis of the first relapse. DFS and OS started with day 1 of treatment at first relapse; DFS ended with progression of disease or death of any cause; OS ended with death. Censoring was done at the date of last contact. For five patients, the exact date of initiation of treatment of relapse was missing. For these patients, date of relapse plus 20 days (median difference in patients with both dates available) was taken as the starting date.

RESULTS

Overall, information on 203 patients with CSI seminoma with relapses after adjuvant carboplatin was collected. Data from nine patients were excluded because of lack of important information (eg, time of relapse, treatment modality used as treatment of relapse). Nine additional patients were excluded because at the time of suspected relapse a contralateral seminoma had been diagnosed.

In these latter patients, a clear distinction between metastases from the contralateral cancer versus a true relapse from the incident primary tumor could not be made. In summary, 185 patients with a median follow-up of 53 months (95% CI, 48 to 60 months) were considered eligible and included in the analysis.

Figure 1 shows an overview of the patient cohorts and their respective outcomes. The median time to relapse was 19 months (95% CI, 17 to 23 months); 118 (64%; 95% CI, 56% to 71%) of 185 relapses occurred during the first 2 years after adjuvant treatment. However, 39 (21%; 95% CI, 15% to 28%) relapses occurred between 2 and 3 years, and 28 (15%; 95% CI, 10% to 21%) were reported after 3 years. The earliest relapse was documented 4 months after orchiectomy, the latest relapse occurred after 15 years.

Mode of Detection, Relapse Pattern, and Treatments After Adjuvant Carboplatin

Table 1 lists the characteristics of patients at the time of relapse after adjuvant carboplatin. Relapses were detected by routine follow-up in 137 (79%) of 173 patients for whom this information was available; in only 36 (21%) patients, detection of relapse was triggered by suspicion as judged by the treating physicians. Of 184 patients, relapses first became evident by computed tomography scan or magnetic resonance imaging in 117 (64%), by clinical signs or symptoms in 28 (15%), and by increasing levels of lactate dehydrogenase or human chorionic gonadotropin in 23 (13%). Positron emission tomography scan or other imaging modalities (eg, x-ray, ultrasound) were infrequently used and provided the first evidence of relapse in only five (3%) and 11 (6%) patients, respectively. In one patient, no mode of initial detection of relapse was documented.

Of 182 patients, stage at relapse was IIB in 88 (48%), IIA in 35 (19%), and IIC in 31 (17%). Only 28 (15%) patients presented with stage III disease. No stage was documented in the remaining three patients. Location and frequency of metastases are listed in Appendix Table A1 (online only).

Table 1. Characteristics at Baseline, Relapse, and Current Status

Characteristic	Proportion (%)
Median age (range), years	38 (19-68)
Method used for carboplatin dosing	
Radionuclides	78 of 150 (52)
24-h urine collection	12 of 150 (8)
Serum creatinine–based approximation	60 of 150 (40)
Unknown	35
Cycles of adjuvant carboplatin	
One	147 of 183 (80)
Two	36 of 183 (20)
Unknown	2
Time to relapse	
Median months (range)	19 (4-184)
During year 1	41 of 185 (22)
During year 2	77 of 185 (42)
During year 3	39 of 185 (21)
After year 3	28 of 185 (15)
First evidence of relapse	
Clinical symptoms/signs	28 of 184 (15)
Markers	23 of 184 (13)
CT scan/MRI	117 of 184 (64)
PET scan	5 of 184 (3)
X-ray/ultrasound	11 of 184 (6)
Unknown	1
Stage at relapse	
IIA	35 of 182 (19)
IIB	88 of 182 (48)
IIC	31 of 182 (17)
III	28 of 182 (15)
Unknown	3
IGCCCG prognostic group	
Good	181 of 185 (98)
Intermediate	4 of 185 (2)
Second relapse	
No	156 of 184 (85)
Yes	28 of 184 (15)
Unknown	1
Status at last follow-up, No.	
Alive without disease	174
Alive with disease	4
Death, disease related	3
Death, probably therapy related	2*
Death, other cause	2†

Abbreviations: CT, computed tomography; IGCCCG, International Germ Cell Cancer Collaborative Group; MRI, magnetic resonance imaging; PET, positron emission tomography.
*One secondary leukemia, one treatment related not specified.
†One each myocardial infarction and chronic obstructive pulmonary disease.

According to the IGCCCG classification, all but four patients had a relapse with good prognosis disease. The four patients with intermediate prognosis disease relapsed 10, 24, 27, and 36 months after orchiectomy. Details of these patients are listed in Appendix Table A2 (online only). Three additional patients were considered to have intermediate prognosis disease by their treating physicians based on elevated lactate dehydrogenase levels but were reclassified as good prognosis for the purpose of the present analysis because in seminoma, the IGCCCG classification uses nonpulmonary visceral metastases as the sole criterion for intermediate prognosis.

Details of the treatments given at the time of relapse after adjuvant carboplatin are shown in Figure 2. The majority of the 185 patients (156 [84%]) received chemotherapy alone; 14 (8%) were treated with a combination of chemotherapy plus local treatment (radiotherapy or surgery; Fig 2A). Local treatment without chemotherapy was rarely used, wherein 11 (6%) patients received radiotherapy alone and four (2%) underwent surgery as their only treatment. Of the 156 patients who received chemotherapy alone, the regimen comprised three cycles of bleomycin, etoposide, cisplatin (BEP) in 56 (36%) and four cycles of etoposide, cisplatin (EP) in 52 (33%; Fig 2B). Four cycles of BEP were used in 16 (10%) patients (13 good prognosis, three intermediate prognosis), and 32 (21%) patients were treated with other combinations/schedules, which are listed in Appendix Table A3 (online only).

Overall, 28 (15%; 95% CI, 10% to 21%) of 185 patients experienced a subsequent relapse. Of those, 27 had previously been classified as IGCCCG good prognosis and only one as intermediate prognosis (Fig 1). The median time from diagnosis of the first relapse to diagnosis of the second relapse was 9 months (95% CI, 7 to 16 months). Characteristics of treatment and outcome in patients with subsequent relapses are listed in Table 2. More second relapses, 10 (28%; 95% CI, 14% to 45%) of 36, were observed in patients who had received two cycles of adjuvant carboplatin compared with 18 (12%; 95% CI, 7% to 19%) of 146 in patients who had received a single cycle of adjuvant carboplatin ($P = .04$, Fisher exact test).

At the time of last follow-up, five of the patients with a second relapse died, three as a result of progressing seminoma, and two as a result of other causes. Four patients were alive with disease, and 19 were alive without disease.

Survival

At the time of last follow-up, 174 (94%; 95% CI, 90% to 97%) of 185 patients were alive without evidence of disease; four (2%) were reported to be alive with persisting disease. Seven (3%) patients died, three as a result of progressing seminoma and two as a result of possible treatment-related causes (one secondary leukemia, one treatment related without further specification). Two patients died as a result of other causes as assessed by their local physicians (one myocardial infarction, one chronic obstructive pulmonary disease). However, a relationship between these two latter deaths and treatment of seminoma cannot be ruled out. Details on the patients who died as a result of other causes are listed in Appendix Table A4 (online only). Figure 3A shows the DFS and OS probabilities after treatment of relapse for all patients. The 5-year DFS was 82% (95% CI, 77% to 89%), and the 5-year OS was 98% (95% CI, 95% to 100%) in the entire cohort of 185 patients. In the subgroup of 111 (60%) patients who received only standard chemotherapy according to their stage and prognostic IGCCCG group, outcomes were similar, with a 5-year DFS of 82% (95% CI, 74% to 91%) and a 5-year OS of 97% (95% CI, 93% to 100%; Fig 3B). Standard chemotherapy treatment of patients with IGCCCG good prognosis was defined as three cycles of BEP or four cycles of EP (n = 108) and for patients with IGCCCG intermediate prognosis as four cycles of BEP (n = 3).

A trend for a worse DFS (hazard ratio, 2.0; 95% CI, 0.9 to 4.4; $P = .07$) was observed in patients who had received two cycles of

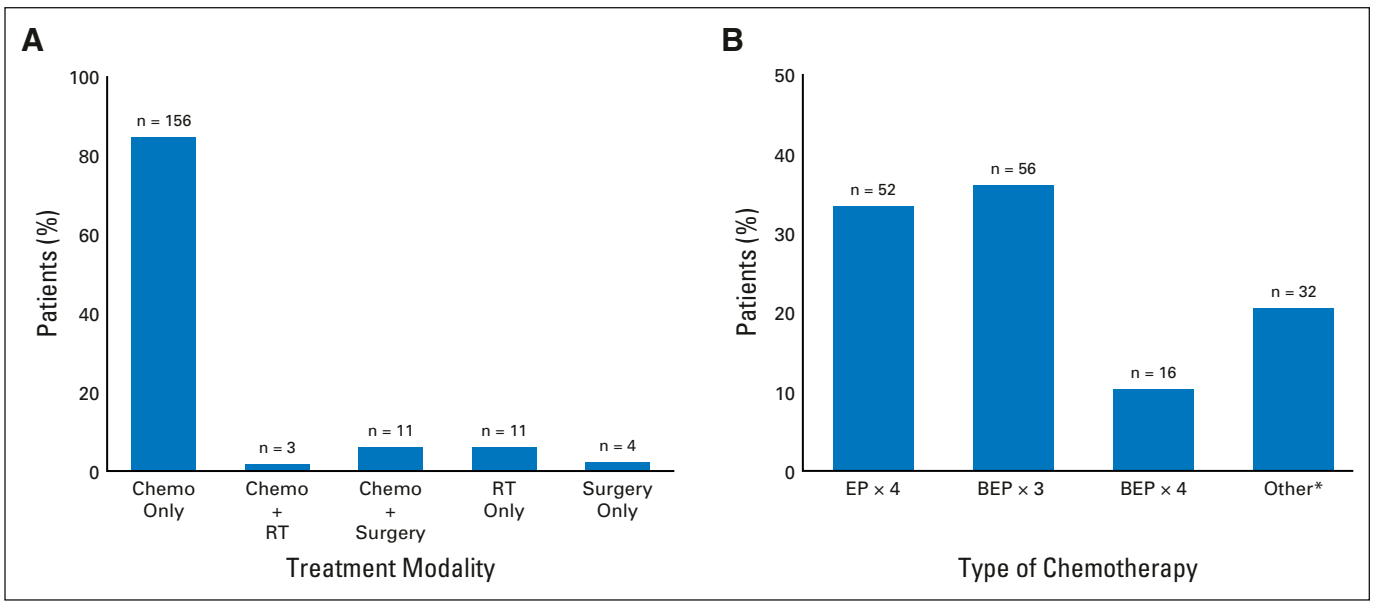

Fig 2. Treatment of first relapse. (A) Treatment modality used in first relapse. (B) Type of chemotherapy chosen for patients treated only with chemotherapy in first relapse. (*) Other schedules used are listed in detail in Appendix Table A3 (online only). BEP × 3, three cycles of bleomycin, etoposide, cisplatin; BEP × 4, four cycles of bleomycin, etoposide, cisplatin; EP × 4, four cycles of etoposide, cisplatin; RT, radiotherapy.

Table 2. Characteristics, Treatment, and Outcome of Patients With Subsequent Relapse

IGCCCG Group	Stage	Elevated Markers	DFI (months)	Therapy in First Relapse (No. of cycles)	Best Response	Therapy in Second Relapse	Status at Last Follow-Up
Intermediate	III	Yes	10	BEP × 4	PR *m+*	TIP × 3	Death as a result of PD
Good	III	Yes	27	BEP × 3*	PR *m−*	Chemotherapy not specified	Alive with disease
Good	III	Yes	162	EP × 4	PR *m−*	TIP × 4	Death as a result of PD
Good	IIA	Yes	8	BEP × 3	CR	Radiation only	Alive without disease
Good	IIC	No	63	EP × 4	CR	TIP × 4 and radiation	Alive without disease
Good	NA	Yes	15	EP × 4	CR	VIP × 4	Alive without disease
Good	III	No	134	BEP × 4	SD	NA (treatment in other institution)	Alive without disease
Good	IIB	No	5	EP × 4	PR *m−*	VIP × 2	Alive without disease
Good	IIC	Yes	8	BEP × 3	PR *m−*	TIP × 3 and surgery	Alive without disease
Good	III	No	14	BEP × 3	PR *m−*	Radiation only	Further relapse, afterward alive without disease
Good	IIB	No	12	Radiation only	CR	EP × 3 + one cycle etoposide + carboplatin	Death of myocardial infarction
Good	IIC	Yes	13	BEP × 4	PR *m−*	TIP × 4 and radiation	Alive without disease
Good	IIC	Yes	107	BEP × 4	PR *m−*	TIP × 4	Alive without disease
Good	IIB	No	6	EP × 4	CR	Radiation and surgery	Further relapse, afterward alive without disease
Good	IIC	Yes	30	BEP × 3	CR	Surgery only	Further relapse, afterward alive without disease
Good	IIC	Yes	11	BEP × 3	PR *m+*	High-dose chemotherapy	Further relapse, alive with disease
Good	IIB	No	12	BEP × 4 and surgery	CR	Radiation only	Further relapse, alive with disease
Good	IIB	No	4	BEP × 3	CR	Surgery only	Further relapse, afterward alive without disease
Good	IIB	No	8	EP × 4	CR	TIP × 3 and surgery	Alive without disease
Good	IIB	Yes	24	Radiation only	CR	EP × 4	Alive without disease
Good	IIC	Yes	29	BEP × 3, CEB × 1	PR *m−*	TIP × 4 and radiation	Alive without disease
Good	IIB	No	12	BEP × 3	CR	VIP × 2 and radiation	Alive without disease
Good	IIB	No	7	BEP × 3	CR	TIP × 4	Alive without disease
Good	III	Yes	18	BEP × 3, EP × 1	CR	Oral etoposide, VIP, high dose	Death as a result of secondary leukemia
Good	IIC	Yes	22	BEP × 3, EP × 1	PR *m−*	Oxaliplatin, actinomycin, high-dose methotrexate, paclitaxel × 4	Alive without disease
Good	IIC	Yes	12	BEP × 4 and surgery	CR	VIP × 4	Further relapse, alive with disease
Good	IIB	No	15	BEP × 3	PR *m−*	High-dose chemotherapy	Further relapse, death as a result of PD
Good	IIB	No	9	BEP × 4 and surgery	CR	TIP × 4 and surgery	Alive without disease

Abbreviations: BEP, bleomycin, etoposide, cisplatin; CEB, carboplatin, etoposide, bleomycin, CR, complete remission; DFI, disease-free interval between adjuvant carboplatin and manifestation of first relapse; EP, etoposide, cisplatin; *m−*, negative marker; *m+*, positive marker; NA, not applicable; PD, progressive disease; PR, partial remission; SD, stable disease; TIP, paclitaxel, ifosfamide, cisplatin; VIP, etoposide, ifosfamide, cisplatin.
*Intended cycle 4 not administered because of the patient's wish as a result of complications; bleomycin not fully dosed in cycle 3.

adjuvant carboplatin, but no difference in OS was seen (data not shown). In addition, we observed a statistically nonsignificant negative trend for an inferior DFS in patients who experienced a relapse < 12 months after orchiectomy and adjuvant treatment (hazard ratio, 1.9; 95% CI, 0.9 to 4.1). However, too few events were observed to draw conclusions with respect to time of relapse and correlation with OS.

DISCUSSION

In this large retrospective analysis in 185 patients who had a relapse after one or two cycles of adjuvant carboplatin for CSI seminoma, we found that such patients still have excellent survival probabilities, similar to patients with de novo metastatic disease. With a median follow-up of 53 months, we found a 5-year DFS of 82% and a 5-year OS of 98%. Only three patients died as a result of progressive seminoma, and two patients died as a result of possible treatment-related causes. For two other patients reported to have died as a result of other causes by their treating physicians, a relation to seminoma treatment could not be ruled out with certainty. These results correspond favorably to the IGCCCG population. In the IGCCCG data set,[14] patients with de novo metastatic seminoma in the good prognosis group had a 5-year DFS probability of 82% and a 5-year OS probability of only 86%. Even compared with more modern patient series in metastatic seminoma with a better 5-year OS of approximately 95%,[15-17] the outcomes found in the current series of patients pretreated with adjuvant carboplatin are still similar. These results demonstrate for the first time to our knowledge that in CSI seminoma, survival probabilities are not impaired after adjuvant carboplatin, even in patients who relapse despite such treatment.

Of note, more relapses occurred in patients who received two cycles of carboplatin. This result should be interpreted with caution because of the retrospective nature of the study, potential biases, and the small number of patients and events. Still, these data do not seem to support the use of two cycles of carboplatin in the adjuvant setting.

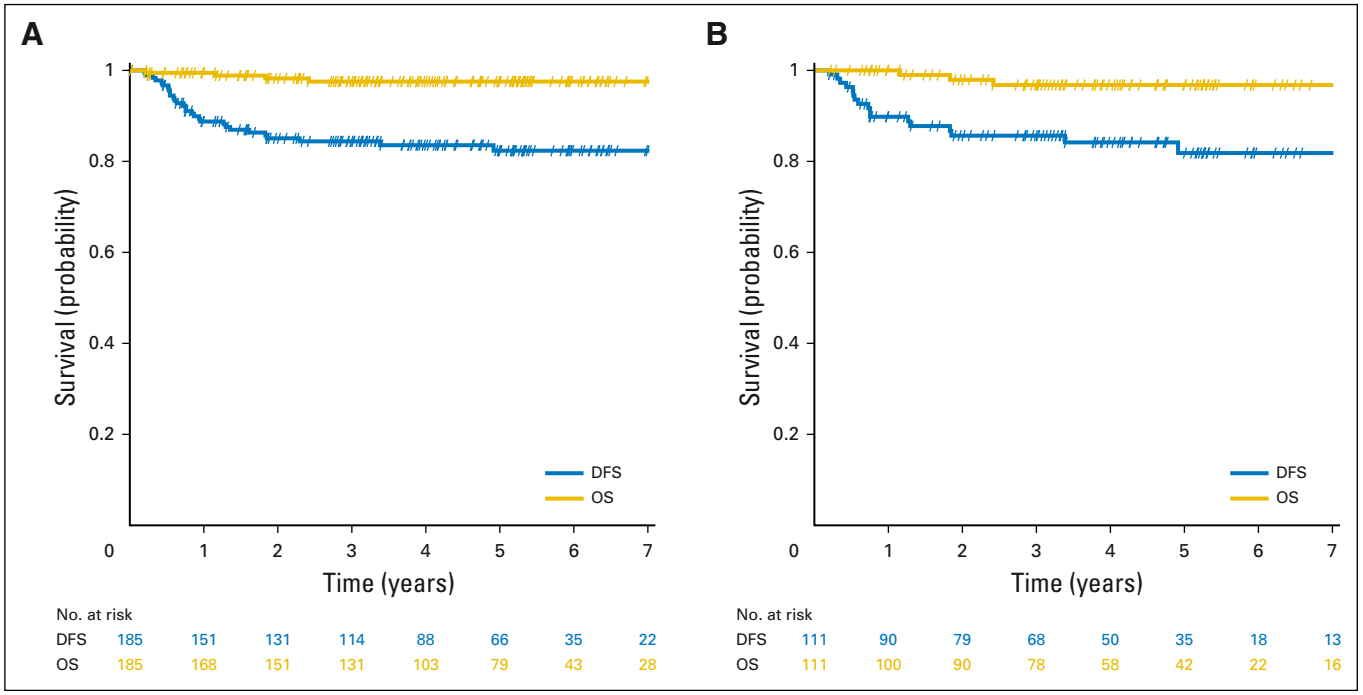

Fig 3. Overall survival (OS) and disease-free survival (DFS) for all patients and for patients who received standard therapy for their stage and prognostic category at first relapse. (A) DFS and OS for all patients. (B) DFS and OS for patients with good prognosis treated with three cycles of bleomycin, etoposide, cisplatin or four cycles of etoposide, cisplatin and patients with intermediate prognosis treated with four cycles of bleomycin, etoposide, cisplatin or four cycles of etoposide, ifosfamide, cisplatin.

In the absence of a prospective randomized trial, the optimal treatment of relapses after adjuvant carboplatin remains unknown. However, in this series, conventional dose chemotherapy with either EP or BEP, which would have been adequate standard treatment of patients with de novo metastatic disease, was used in the majority of patients who relapsed. In the remaining patients, either a combination of chemotherapy plus local surgery (n = 11) or radiation (n = 3), local radiation alone (n = 11), or surgery alone (n = 4) had been applied. On the basis of this information, we suggest that patients who relapse after adjuvant carboplatin should be treated identically to patients with de-novo metastatic disease.

The median time to first relapse after adjuvant carboplatin was 19 months in this series. In accordance with previous reports,[16] the majority of first relapses occurred in the retroperitoneum and were detected by computed tomography scan or magnetic resonance imaging during routine follow-up. Self-reported symptoms, clinical signs, or elevated tumor markers were noticed as the first evidence of relapse in only a minority of patients. Of note, more than one third of patients had a relapse beyond a follow-up period of 2 years, and 15% relapsed beyond a follow-up period of 3 years. This finding suggests that compared with active surveillance, adjuvant treatment with carboplatin may delay relapses. Kollmannsberger et al[15] studied active surveillance in CSI seminoma and reported a median time to relapse of 14 months, with only 8% relapses occurring beyond 3 years. A prospective population-based study by Tandstad et al[17] used a risk-adapted approach. Patients managed by active surveillance had a median time to relapse of 1.3 years, and 17% of the relapses occurred > 2 years after orchiectomy. Patients managed with adjuvant carboplatin had a median time to relapse of 1.7 years, and 33% of the relapses occurred > 2 years after orchiectomy. In the largest published series by Mortensen et al,[16] the median time to relapse in 1,954 patients with CSI seminoma treated with active surveillance was 13.7 months, but 22% of relapses occurred between 3 and 5 years and 4% > 5 years after orchiectomy. Similar results were reported by the German Testicular Cancer Group.[10] Taken together, these data indicate that although adjuvant carboplatin will reduce the risk of relapse in CSI seminoma compared with active surveillance, prolonged follow-up beyond 3 years may be required in patients after adjuvant treatment.[18]

In the present series, 28 (15%) of 185 patients treated for their first relapse after adjuvant carboplatin experienced a second relapse. This rate is similar to a 14% second relapse rate from a retrospective analysis of patients treated with adjuvant carboplatin in south central England, which is included in the present series,[11] and similar to patients treated for de novo metastatic seminoma. Surveillance studies, however, reported lower second relapse rates. Kollmannsberger et al[15] reported a 4% second relapse rate in CSI seminoma after initial active surveillance and subsequent cisplatin-based first-line chemotherapy with a similar median follow-up of 52 months compared with the current series. In the study by Mortensen et al,[16] only eight (6%) of 136 patients who experienced a relapse during active surveillance and received treatment with BEP had a second relapse. Similarly, the Swedish and Norwegian Testicular Cancer Group[19] observed only one second relapse among 65 patients with CSI seminoma who underwent active surveillance as initial management. This higher rate of subsequent relapses and the more-frequent need for further salvage treatment needs to be studied further.

Patient selection and different patient populations at first relapse might explain these discrepancies. First, adjuvant carboplatin is primarily used in patients with one or more risk factors, which reflects more-advanced and/or more-aggressive disease.[17,20] Second, because we analyzed only patients who relapsed after carboplatin treatment, this series might have selected patients with biologically more unfavorable disease as a result of carboplatin

resistance. However, it is conceivable that adjuvant carboplatin may induce some form of cisplatin resistance and may reduce subsequent activity of this drug if further chemotherapy is needed. Second relapses in this series, however, could successfully be salvaged with further treatment in the majority of patients.

In conclusion, this study has all the limitations of a retrospective analysis. Most importantly, because we studied only patients with relapses after adjuvant carboplatin, we cannot comment on the entire population of patients with CSI seminoma from whom the current study sample was drawn. We also cannot comment on the overall risks and benefits of adjuvant carboplatin versus active surveillance. However, for the first time in our knowledge, we demonstrate that adjuvant carboplatin is safe, even in patients who experience a relapse after such treatment. The majority of patients with CSI seminoma who experienced a relapse after adjuvant carboplatin could successfully undergo salvage therapy with excellent survival probabilities by using the treatment algorithms established for de novo metastatic disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

AUTHOR CONTRIBUTIONS

Conception and design: Stefanie Fischer, Dirk Klingbiel, Jörg Beyer, Silke Gillessen
Administrative support: Stefanie Fischer, Silke Gillessen
Provision of study materials and patients: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Appendix

Table A1. Frequency and Distribution of Metastases in First Relapse

	No. of Patients
Presence of lymph node metastases*	
Retroperitoneal	166
Paratracheal/mediastinal	16
Inguinal	10
Supraclavicular	3
Axillary	2
Retrocrural	2
Cervical	1
Presence of visceral metastases*	
Lung	4
Liver	3
Bone	1
Occurrence of multiple metastases in one patient	
Lymph nodes and visceral	6
Lung and lymph nodes	3
Liver and lymph nodes	2
Lung, liver, and lymph nodes	1
Lymph nodes and soft tissue/muscle	1
Multiple lymph node locations	14
Lymph nodes, retroperitoneal and mediastinal	7
Lymph nodes, retroperitoneal and other	6
Lymph nodes, retroperitoneal, mediastinal, and other	1

*Multiple locations possible.

Table A2. Characteristics at Baseline, Treatment and Outcome of Patients With IGCCCG Intermediate Prognosis

IGCCCG	Age (years)	Cycles of Carboplatin	Dosing Method	Localization of Metastases	b-HCG Elevated	LDH Elevated	Treatment (No. of cycles)	Subsequent Relapse	Treatment (No. of cycles)	Last Status
Intermediate	44	1	Cockcroft Gault	Bone	No	Yes	BEP × 3 VIP × 1	No	NA	Alive w/o
Intermediate	48	1	Radionuclides	LN retroperitoneal, mediastinal, axillary, liver	Yes	Yes	BEP × 4	No	NA	Alive w/o
Intermediate	25	1	Wright formula	LN mediastinal, lung, liver	Yes	No	BEP × 4	No	NA	Alive w/o
Intermediate	24	2	Cockcroft Gault	LN neck, liver	Yes	Yes	BEP × 4	Yes	TIP × 3	Death as a result of PD

Abbreviations: BEP, bleomycin, etoposide, cisplatin; b-HCG, β-human chorionic gonadotropin; IGCCCG, International Germ Cell Cancer Collaborative Group; LDH, lactate dehydrogenase; LN, lymph node; NA, not applicable; PD, progressive disease; TIP, paclitaxel, ifosfamide, cisplatin; VIP, etoposide, ifosfamide, cisplatin; w/o, without disease.

Table A3. Other Types/Schedules of Therapy Chosen for Treatment of First Relapse

Therapy (No. of cycles)	No. of Patients
Chemotherapy only	
EP × 3	16
BEP (cycles unknown)	1
I-BEP × 3	1
BEP × 3 + VIP × 1	1
BEP × 2 + EP × 2	2
BEP × 3 + EP × 1	5
BEP × 2 + EP ×1	1
BEP × 1 + EP × 3	2
EP × 3 + etoposide/carboplatin AUC 7 × 1	1
BEP × 3 + CEB × 1	1
VIP × 4	1
Chemotherapy and local treatment	
BEP × 3 + RT	1
EP × 1 + RT	1
Carboplatin AUC 7 × 2 + RT	1
BEP × 4 + surgery	3
BEP × 3 + surgery	2
BEP × 2 + surgery	1
EP × 4 + surgery	3
VIP × 3 + surgery	1
VIP × 2, EP × 4 + surgery	1

Abbreviations: AUC, area under the curve; BEP, bleomycin, etoposide, cisplatin; CEB, carboplatin, etoposide, bleomycin; EP, etoposide, cisplatin; I-BEP, ifosfamide, bleomycin, etoposide, cisplatin; RT, radiotherapy; VIP, etoposide, ifosfamide, cisplatin.

Table A4. Characteristics of Patients Who Died as a Result of Other Causes

Patient	Age at Adjuvant Carboplatin (years)	Time to Relapse (months)	Treatment of Relapse (No. of cycles)	Subsequent Relapse	Treatment (No. of cycles)	Best Response	Approximate Time From End of Treatment to Death (years)
Death as a result of MI	58	12	Radiation only	Yes	EP × 3 + carboplatin × 1, etoposide	CR	7
Death as a result of COPD	64	23	BEP × 1, EP × 3	No	NA	CR	14

Abbreviations: BEP, bleomycin, etoposide, cisplatin; COPD, chronic obstructive pulmonary disease; CR, complete remission; EP, etoposide, cisplatin; MI, myocardial infarction; NA, not applicable.